Allergy Abstracts

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Asthma and Hay Fever

The Role of Chlorpromazine in the Treatment of Bronchial Asthma and Chronic Pulmonary Emphysema. Baum, G. L., Schotz, S. A., Gumpel, R. C., and Osgood, C.: Dis. Chest **32**: 574, 1957.

Ten patients with uncomplicated bronchial asthma, 6 with bronchial asthma and chronic pulmonary emphysema, and 19 with primary chronic diffuse obstructive pulmonary emphysema received a single intramuscular dose of 25 to 50 mg. of chlorpromazine. In some instances, this drug was administered orally or intramuscularly in combination with therapy designed to improve pulmonary ventilation and arterial blood gas content. These measures included IPPB with oxygen, antibiotics, expectorants, aminophylline, mechanical elimination of bronchial secretions, and, in some instances, adrenocortical steroids and Diamox. Twenty-one patients with chronic diffuse obstructive pulmonary emphysema were also studied in the laboratory under basal conditions. Measurements were made in the changes in mean values for minute

volume of respiration, arterial oxygen saturation, carbon-dioxide tension, and pH. A single 25 mg. intramuscular injection of chlorpromazine in 10 patients with uncomplicated bronchial asthma was followed within 15 to 30 minutes by marked diminution of wheezing and restlessness in 5 instances. One of these patients maintained a satisfactory course when the oral preparation was combined with a bronchodilator and expectorant for the following 6 days. No change occurred in 2 subjects within an hour after injection. Chlorpromazine combined with other therapy was beneficial in 3 cases. Only one of 6 patients with bronchial asthma and pulmonary emphysema who received a single intramuscular dose showed a distinct lessening of dyspnea and wheezing. Similar benefits occurred in 2 patients when the drug was combined with conventional bronchodilator therapy. Of 19 patients with primary chronic diffuse obstructive pulmonary emphysema, relief of respiratory embarrassment with wheezing and cyanosis was observed in 1 case when chlorpromazine was administered as a single intramuscular dose. Eight patients exhibited a favorable response when chlorpromazine was combined with other forms of therapy. Despite adequate relaxation, clinical improvement was not attained by intensive therapy in 9 patients. Five of these patients died after receiving chlorpromazine for 3 to 33 days. In view of the severity of the disease in this group, no harmful effect could be attributed to chlorpromazine therapy. No instance of jaundice or leukopenia was noted in this series of 35 patients. Of 21 patients with chronic diffuse obstructive pulmonary emphysema, drowsiness occurred in 19 within 1 hour after the administration of 25 to 50 mg. of chlorpromazine intramuscularly. No significant changes were noted in the mean values for minute volume of respiration, the arterial oxygen saturation, carbon dioxide tension, and pH. The clinical status of 1 patient became alarming within 1 hour after drug administration. There was increased respiratory embarrassment and a state of semi-stupor. This patient responded to IPPB with oxygen therapy. Only 2 subjects exhibited falls of over 20 mm. Hg in diastolic pressure. It was concluded that chlorpromazine may be safely and effectively administered, either alone or in combination with known bronchodilator agents, for the relief of paroxysms of bronchial asthma. In chronic pulmonary emphysema, chlorpromazine appears to be a useful adjunct in combination with intensive therapy designed to correct pulmonary ventilation. E. W.

The Diagnosis of Asthma in Infancy. Buffum, W. P.: J. Pediat. **52**: 264, 1958.

The case records of 79 children with recurrent wheezing, all seen before the age of 2 and followed for a period of at least two years, were reviewed. Fifty-two of the patients showed definite signs of allergy. Seventeen others had presumptive signs of the allergic state, such as a positive family history and a blood eosinophilia of at least 6 per cent. All of the 10 remaining patients in the series had recurrent wheezing but no other signs of allergy. In the first group of 52 cases with demonstrable allergy, 60 per cent had some wheezing during the last year of observation. In the second group of 17 patients with only circumstantial evidence of allergy, 70 per cent were entirely well for the last year. Of the 10 patients with no signs of allergic disease other than the repeated mild wheezing, 80 per cent were entirely well at the end of the last year of observation. These findings seemed to indicate that the more marked the evidences of allergy, the worse the prognosis. Of 18 patients who had had eczema and positive reactions to scratch tests, 72 per cent were still sick during the last year of observation. There were 19 infants with a positive scratch reaction to egg, and 17 of these had some wheezing during the last year of

observation. The records of the 6 cases in the series which were most difficult to control revealed that all had had eczema and had manifested positive skin reactions, strongly positive ones to egg. Positive skin reactions appeared to increase with advancing age. Of the patients with negative or doubtful scratch reactions about half, when retested a year later, showed definite positive reactions, usually to inhalants. Those patients who originally had positive reactions to foods showed a definite diminution in reactivity to these extracts and an increase in positive inhalant reactions. Usually those patients with multiple reactions or with strongly positive reactions had more severe symptoms. Contrary to the generally accepted opinion that asthma in the beginning manifests itself in paroxysmal attacks with complete clearing in the intervals, the patients in this series began with what was apparently a respiratory infection and then wheezed continuously for periods of from one to several months. This occurred in the group with proved allergies and also in the group with no proved allergies. Treatment of the allergy, including control of environment, was strikingly successful in most of the doubtful cases of asthma. H. F.

Triamcinolone (Aristocort), New Corticosteroid Hormone: Its Use in Treatment of Allergic Disease. Feinberg, S. M., Feinberg, A. R., and Fisherman, E. W.: J. A. M. A. **167**: 58, 1958.

Triamcinolone was administered to 70 patients for periods varying from a few days to 40 weeks. The age of the patients varied from 7 to 74 years. In the group there were 52 patients with asthma, mostly of the chronic intractable type of unknown etiology. Other patients had various types of allergic dermatoses, seasonal hay fever, and perennial vasomotor rhinitis. The initial 24-hour dose of the steroid varied from 8 to 16 mg., and the maintenance dose ranged from 2 to 8 mg. Good therapeutic effects were obtained with about one-half the dosage required for prednisone. Aristocort produced most of the usual steroid hormone side effects. In addition, a few patients developed a peculiar syndrome of headache, sleepiness, dizziness, and weakness which was not relieved by the addition of supplementary electrolytes. Unlike some of the other steroids, Aristocort was found to be a diuretic and a sodium-depleting hormone. This action was considered advantageous in treating allergic patients who also had cardiac conditions or hypertension. M. C.

Prednisolone Aerosol in Asthmatic Bronchitis. Peters, G. A., and Henderson, L. L.: Proc. Staff Meet., Mayo Clin. **33**: 57, 1958.

An aerosol mixture consisting of 0.25 ml. of prednisolone phosphate and 0.25 ml. of 1:200 isoprophylarterenol hydrochloride (Isuprel) was given by nebulization to 11 patients with bronchial asthma who were persistently coughing and wheezing. Four to six treatments were administered daily for 4 to 25 days. No untoward effects were noted. Ten of the 11 patients appeared to be benefited. Use of conventional measures already in force was continued. Although the improvement which occurred appeared to be less striking than could be expected with systemic therapy, it was suggested that this new form of therapy might prove to be a useful adjunct in the management of asthma, since only small amounts of steroids (not more than 7.5 mg.) are used per day. The likelihood of any appreciable absorption of steroid is minimal with such dosage, and this would eliminate the risk of side reactions usually associated with steroid therapy. M. C.

Studies in Atmospheric Pollen in Jerusalem in 1953-1954. Parog, Y., Feinbrun, N., and Tas, J.: Bull. Research Council of Israel, Section D Botany (August, 1957).

Air-borne pollens were identified and counted by the standard (Durham) technique from March, 1953, to March, 1954, at two stations in Jerusalem. The pollens identified were: (a) *Cupressus, Pinus,* and *Poterium spinosium* (February-April); (b) *Morus nigra, Olea europaea,* and grasses (April-May); and (c) *Casuarina* and *Ceratonia siliqua* in much smaller quantities (September-October).

On the basis of the high counts of olive pollen obtained, the authors suggest that this plant is not only insect-pollinated but also wind-pollinated. Wind pollination probably occurs at the later stage of anthesis of each flower when the pollen becomes dry and dusty. I. G.

Dermatology

Dermatitis Caused by a Copying Paper. Kendrick, F. J.: Arch. Dermat. **77**: 334, 1958.

The author observed severe contact dermatitis in six male office workers who were employed in the billing department of a large corporation. The lesions were typical of contact eczema, being vesicular in type with crusting patches on the dorsa of the hands and forearms. In 2 patients there were lesions on the face and neck. Patch tests were done with routine office contactants, such as carbon paper, cleansers, typewriter ribbon, and Thermo-Fax copying paper. After 48 hours all the tests were negative except the one to the Thermo-Fax copying paper. A vesicular response developed within 6 to 24 hours on the test site under the Thermo-Fax copying paper and caused so much discomfort that the patients had to remove the test patches. All the subjects had been employees of long standing, and none had had any new exposures or changes in their working conditions that could have been responsible for their rash except for the introduction of this type of copying paper. The patients responded poorly to the usual type of bland therapy, became worse as the contact with the copying paper continued, and eventually had to be removed from the job before the rash subsided. Because of frequent difficulty with eczematoid dermatitis from this type of Thermo-Fax copying paper, the company making this product introduced a new form of copying paper. All six patients were patch tested with the new paper and showed negative reactions to it. The author subsequently learned that the old paper contained tertiary butyl catechol, which apparently was the chemical responsible for producing the severe contact dermatitis. R. W.

Miscellaneous Allergies

Follow-up Study of Fatal Penicillin Reactions. Rosenthal, A.: J. A. M. A. **167**: 1118, 1958.

During the years 1952 and 1953, the Office of the Chief Medical Examiner of the City of New York investigated 8 fatal reactions which followed the administration of penicillin. In the years between 1954 and 1956, there were 18 additional deaths from the antibiotic, and incomplete returns for 1957 list 4 more deaths. Of the 30 cases, 17 were Caucasians and 13 were Negroes. The youngest patient was 1 month old and the oldest was 66 years old. There were 14 males and 16 females. Six deaths occurred in the home and 12 at physicians' offices. Two patients reacted at home and died soon after arrival at

the hospital; 3 reacted at physicians' offices and died shortly thereafter at hospitals. Seven deaths occurred at hospitals where the injections were given. Reactions were of the immediate type in 25 patients and were delayed in 5. The delayed reactions occurred within 30 minutes in 2 patients, within 20 minutes in 1 patient, within 2 hours in another patient, and after 14 days in another. These patients had received from 200,000 to 500,000 units of penicillin. In 3 cases, antihistamines had been administered simultaneously with the penicillin injection. In 14 cases no inquiry had been made prior to the injection as to whether the patient had previously received penicillin or had had any reaction to the antibiotic. Subsequently, in only 7 cases was it possible to demonstrate a history of known sensitivity. It appeared that there was a definite indication for the use of penicillin in 12 patients. In 13 patients the indication for penicillin was doubtful, and in 5 patients there was no indication for its use. It was noted that the history is not reliable in determining whether or not to give penicillin since sensitization may occur through ingestion of penicillin-contaminated milk or by absorption through the skin of penicillin produced by dermatophytes. The author states that oral penicillin and skin testing with penicillin may cause fatalities and that the advice to use antihistamine with penicillin for purposes of protection against severe reactions is misleading. M. C.

Anaphylactoid Reaction to Nitrofurantoin. Fisk, A. A.: New England J. Med. **256**: 1054, 1957.

Nitrofurantoin (Furadantin) appeared to be the etiological factor in the production of an anaphylactoid reaction in a 59-year-old man. He had received one course of this medication for chronic prostatitis. Six months later the drug was administered again in doses of 0.1 Gm. four times a day. Four days later the drug was voluntarily discontinued because of weakness and a temperature of 101° F. Three days later the patient took one tablet of nitrofurantoin at bedtime and several hours later he was seized with a violent headache and severe epigastric pain radiating across both sides of the chest and down both arms. He became dyspneic, vomited, and complained of weakness. He was admitted to the hospital with a diagnosis of probable myocardial infarction. On admission to the hospital, his temperature was 103.4° F. and his blood pressure was 130/80. Physical examination was negative except for generalized abdominal tenderness. An electrocardiogram showed only sinus tachycardia. The white cell count was 15,200 with one eosinophil in the field. An x-ray of the chest and abdomen was normal. Shortly after admission an erythematous macular rash was noted on both legs. The patient's condition became critical, with marked dyspnea, cold, sweaty extremities, and severe back pain. The blood pressure fell to 86/60 and the pulse was 132. Intravenous administration of morphine, hydrocortisone, and nor-epinephrine resulted in dramatic clinical improvement. The next day the rash disappeared, the temperature was normal, and the patient was discharged. E. W.

Aplastic Anemia After Meprobamate (2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate) Therapy. Meyer, L. M., Heeve, W. L., and Bertscher, R. W.: New England J. Med. **256**: 1232, 1957.

Aplastic anemia after meprobamate therapy (Miltown) occurred in a 28-year-old woman. This patient had ingested 1200 mg. of meprobamate over an 8-day period. One week later she developed purpuric areas over the arms and legs. She then noted bleeding of the gums and nose and the onset of profuse menstrual flow. Physical examination revealed marked pallor, ecchymoses of all extremities, swollen, ulcerated, bleeding gums, enlarged, tender

submental and submaxillary lymph nodes, and profuse vaginal bleeding. The temperature was 103° F., pulse 120, and respirations 25. The hemoglobin was 6.4 Gm., and the red count was 2,260,000. This rose to 10.65 Gm. and 3,630,000 six days after admission. Bone-marrow aspiration revealed severe hypoplasia of all myeloid elements, with only occasional mature lymphocytes. Therapy consisted of transfusions of whole blood, prednisone, penicillin, and streptomycin. Within four days, the menstrual flow lessened, but the gingival ulcer increased in size. The temperature remained elevated at 103° F., and many petechiae appeared over the trunk. The submental lymph nodes became large and tender. By the eleventh hospital day, there seemed to be marked improvement with gradual abatement in the gingival symptoms and the cessation of vaginal bleeding. However, fresh petechiae and purpuric areas appeared thereafter. On the nineteenth hospital day, the patient had a severe chill and an elevation in temperature. She complained of pain in the right side of the chest and expectorated bloody sputum. X-ray examination showed pneumonia of the right upper lung field. Numerous petechiae appeared on the trunk and legs. Vaginal bleeding became profuse, and severe abdominal distention developed within four days. Oral bleeding and petechiae became more extensive. The patient expired 23 days after admission. At autopsy, diffuse hemorrhages were found in the lungs, heart, kidneys, and abdominal muscles. Pneumonitis of the right lung surrounding areas of infarction was observed. The bone marrow of the ribs and vertebrae was hypoplastic. E. W.

Reactions to Benzathine Penicillin. MacFarland, R. B.: New England J. Med. **259**: 62, 1958.

Single intramuscular injections of 600,000 units of benzathine penicillin G were administered to 12,858 Armed Service personnel following their routine inoculations. Recruits with past histories of untoward responses to penicillin were excluded from the study. Reactions appeared in 175 persons (1.3 per cent) and were of the delayed type. Of these, 21 per cent presented dermatologic manifestations, 76 per cent had skin lesions combined with subcutaneous or periarticular swelling, and 8 per cent had reactions that were sufficiently severe to require cortisone therapy. Reactions generally appeared from eight to fifteen days after the injection. "There was no correlation of the interval between injection and reaction and the length or severity of the reaction." Of the 130 patients with serum sickness, 26 experienced relapses. Over 25 per cent of the severe cases had intermittent symptoms for more than 30 days after injection. Antihistamine therapy slightly diminished the duration of the allergic illness. "Relapses were frequent and occurred after placebo or antihistamine therapy as well as after cortisone." It was concluded that this intramuscular preparation of benzathine penicillin G provided an effective and safe method for the administration of penicillin in this large group of men. H. S.

Allergic Accidents Caused by Corticotropin (ACTH). Charpin, J., and Zafiropoulo, A.: Semaine hôp. Paris **34**: 274, 1958.

Eleven allergic patients, 9 of whom had bronchial asthma, developed reactions following the administration of ACTH. In 10 patients, severe urticaria or generalized pruritus with intense flushing occurred. Status asthmaticus ensued in 4 patients and Quincke's edema in another. The allergic reactions occurred after the first injection in 2 patients and after the ninth injection in 1 patient. ACTH of pork origin adsorbed on zinc hydroxide caused

the reactions in 9 of the patients. Preparations of ACTH without delayed absorption and ACTH preparations of sheep and beef origin also caused allergic reactions. Evidence is presented which indicates that the patients were allergic to a protein present in all pituitary extracts regardless of their functional specialization or their animal origin. M. C.

Thrombocytopenic Purpura in a Diabetic Treated With the Hypoglycemiagenic Sulfamide BZ55. Bousser, J., Christol, D., and Bouillier, J. M.: Bull. et mém. Soc. méd. hôp. Paris **73**: 943, 1957.

A 75-year-old diabetic developed an acute thrombocytopenic purpura after taking twenty 500 mg. doses of the antidiabetic sulfamide BZ55 orally over a period of 4 days. The bone marrow counts were normal. The patient recovered within 12 days after receiving transfusions, delta-cortisone, and Aureomycin. Immunohematologic investigations failed to reveal antiplatelet antibodies either in an isolated form or in conjugation with BZ55. I. G.

Otorhinology and Ophthalmology

Comparative Study of Ophthalmic Decongestants in Allergic Conjunctivitis. Tuft, L., and Neish, D. D., Jr.: J. A. M. A. **167**: 60, 1958.

The efficacy of various ophthalmic decongestants was studied in allergic patients in whom ocular symptoms had been induced by the introduction of specific allergens into the eyes. Two drops of the solution being studied were instilled into the conjunctival sac, and the decongestant effect was noted over a period of 10 minutes. A total of 130 comparative tests were made. The following solutions were used in the study: epinephrine (1:1,000 in a proportion of 4 c.c. to 30 c.c. of solution); phenacaine (0.2 per cent) in a solution of equal parts of boric acid and rose water; epinephrine in boric acid and rose water; epinephrine in rose water; phenacaine in boric acid; Estivin; hydrocortisone acetate (0.5 per cent); cortisone acetate (0.5 per cent); cortisone acetate and Chlor-Trimeton; and ephedrine (0.5 per cent) in isotonic sodium chloride.

The results obtained were fairly uniform and allowed for critical evaluation of the drugs. The most effective of these was epinephrine, which produced rapid blanching, obliteration of congestion, and relief of all symptoms in most cases within 5 minutes after instillation. No mydriasis was observed with the concentration of epinephrine used. Rose water seemed to be the best vehicle. Phenacaine lessened burning and itching, but no reduction in congestion was noted. Since this and other local anesthetics are potential sensitizers, it is questionable whether their use is warranted, especially when relief is usually obtainable without them. Estivin appeared to have no more beneficial effect than could be obtained from the use of a simple diluent, such as rose water. "Little or no effect was obtained from the corticoid preparations."
M. C.

Anaphylaxis

Anaphylaxis and the Nervous System. Part II. Szentivanyi, A., and Filipp, G.: Ann. Allergy **16**: 143, 1958.

The Horsley-Clarke stereotaxic technique was employed to produce focal electrolytic lesions of the hypothalamus and other areas of the nervous system of guinea pigs in order to evaluate the effect of such lesions on anaphylactic shock, on local anaphylaxis, and on other allergic reactions. It had been

shown previously that such lesions in the tuberal region of the hypothalamus inhibit the anaphylactic shock phenomenon. In spite of proper precautions and a carefully developed technique, about 50 per cent of the guinea pigs subjected to this operation died within twenty-four to forty-eight hours. Animals which survived the operative procedure regained their preoperative fitness in three to four days.

A series of 147 guinea pigs was sensitized by one subcutaneous injection of 0.2 to 0.3 ml. of undiluted horse serum and then subjected to the above operative procedure on the seventh or eighth day after sensitization. Shock was induced by intravenous reinjection of 0.5 to 1.0 ml. of undiluted horse serum thirteen to fourteen days after the operation. Another group of 68 animals was subjected to the same procedure except that sensitization was carried out just prior to the operative procedure. All 215 animals were grouped together, since no significant differences were noted in the results obtained with these two procedures. A second group which acted as a control series consisted of 48 guinea pigs in which all phases of the operative procedure were carried out except the final stage of applying electrolysis. In a third group there were 58 animals in which the lesions were produced in the supraoptical region of the hypothalamus. In a fourth group, the lesions were produced in the mammillary region of the hypothalamus, while in a fifth group traumatization was produced outside the hypothalamus, in the cortical, thalamic, and mesencephalic regions. A sixth group, consisting of 250 animals, served as a second control and was subjected to no operative procedure. Sensitization and provocation of shock were completely identical with the operated groups. The exact localization of the lesions was established after death of the animals (or sacrifice of the survivors using carbon monoxide), first macroscopically using the stereoscopic microscope and then by histologic examination. In those animals in whom tuberal lesions had been produced, there was a marked diminution in the percentage of anaphylactic shock. Thirteen per cent had fatal reactions, 16 per cent had severe reactions, 18 per cent had mild reactions, and 53 per cent were unaffected. A total of 71 per cent therefore showed little or no reaction to the shocking injection. Only 9 per cent of the animals in whom lesions had been produced in regions other than the tuberal area were protected against anaphylactic shock, and only 4 per cent of the control group failed to show evidence of shock.

It is apparent from these results that the antianaphylactic effect of the operative procedure as described appears to be specifically related to lesions of the tuberal region, strictly circumscribed within the hypothalamus. The simple stabbing of the tuberal area without electrolysis has no such antianaphylactic effect. The Arthus phenomenon produced in rabbits was not affected in any way by the production of tuberal lesions, nor was the development of experimentally produced turpentine eczema prevented by such lesions. Tuberal lesions also failed to prevent the development of the Sanarelli-Shwartzman phenomenon. H. F.

Production of Anaphylaxis in the White Mouse With Soluble Antigen-Antibody Complexes. Tokuda, S., and Weiser, R. S.: Science **127**: 1237, 1958.

Two methods of preparation of soluble antigen-antibody complex were employed in this study. The first method was the mixture of anti-bovine serum albumin (BSA) rabbit serum with 8 times the amount of BSA determined to be present in a precipitate formed in the zone of equivalence. Following incubation of the mixture at 37° C. for 20 minutes, it was cleared by centrifugation. The second method consisted of using excess antigen to dissolve a

precipitate formed in the zone of equivalence. After washing the precipitate, a solution of BSA was added which contained 10 times the amount of antigen present in the precipitate. This mixture was agitated, incubated, and then centrifuged. When doses of the soluble antigen-antibody complex obtained by the first method, containing 0.6 mg. of antibody N, were injected intravenously in white Swiss mice, anaphylactic death occurred in 15 of 16 animals. A dose of soluble complex obtained by the second method, containing 0.48 mg. of antibody N, produced anaphylactic death in 10 of 16 mice. Control studies with BSA in normal serum, anti-BSA serum, bovine gamma globulin in anti-BSA rabbit serum, BSA alone, and supernatant fluids from mixtures of antigen and antibody in the zone of equivalence yielded negative responses.

In another experiment, mice were sensitized with *H. pertussis* vaccine 5 days prior to injection of the antigen-antibody complex. A dose of soluble complex prepared by the first method which contained 0.12 mg. of antibody N caused all 18 pertussis-vaccinated mice to die in anaphylactic shock. Only 5 of 18 nonvaccinated animals died following the same dose of complex.

It is unlikely that the antigen-antibody complexes used dissociated significantly in vivo. Thus, anaphylaxis was probably caused by soluble antigen-antibody complexes acting either within the circulating blood or in surrounding tissues into which they may have diffused. In view of the fact that anaphylaxis produced with soluble antigen-antibody complexes was typical in all respects, it is suggested that "the site of antigen-antibody action and ensuing events leading to anaphylaxis are the same regardless of whether shock is induced in the usual manner by injection of antigen or by the injection of soluble preformed antigen-antibody complexes." B. S.

Pharmacology, Physiology, and Pathology

The Potentiation of Histamine by Imidazoleacrylcholine (Murexine) and Imidazoleproprionylcholine (Dihydromurexine). Tabachnick, I. I. A., and Roth, F. E.: J. Pharmacol. & Exper. Therap. **121**: 191, 1957.

The effects of histamine on strips of guinea pig ileum, guinea pig tracheal chains, and isolated perfused guinea pig lungs were found to be potentiated by imidazoleacrylcholine (ImAcrCh) and imidazoleproprionylcholine (ImPrCh). These compounds did not enhance the action of acetylcholine, of serotonin, or of β-2-pyridylethylamine; nor did they inhibit monamine oxidase, spermine oxidase, or an enzyme from mouse liver known to metabolize histamine. Diamine oxidase, an enzyme that metabolizes histamine, was inhibited by ImAcrCh and by ImPrCh, although not nearly so effectively as by aminoguanidine. It is suggested that it is this inhibition of histamine-destroying enzyme which accounts for the observed histamine potentiation. E. K.

The Effect of Histamine on Neuromyal Blocking Agents. Schenk, E. A., and Anderson, E. G.: J. Pharmacol. & Exper. Therap. **122**: 234, 1958.

Anesthetized cats were prepared so that a tibialis anticus muscle could be stimulated either directly or through the cut end of the peroneal branch of the sciatic nerve. Drugs were administered either intra-arterially or intravenously. Neuromyal blocking agents generally fall into one group which prevents depolarization of the end plate and into another group which maintains depolarization of the end plate. Intravenous histamine given in the presence of a depolarizing type of block failed to affect the block. Close intra-arterial histamine, however, antagonized the block. When nerve block was produced by a nondepolarizing agent (d-tubocurarine), histamine markedly

prolonged the duration and increased the depth of the block. Neither blood pressure changes nor released epinephrine was related to these changes. Continued administration of histamine rapidly led to tachyphylaxis of blood pressure response, but the neuromyal effects remained undiminished. Antihistamines prevented or reduced the blood pressure fall from histamine but did not affect the neuromyal action. Bilateral adrenalectomy of the cats failed to alter the neuromyal response. It is proposed that "histamine does have an effect directly on the neuromyal events associated with blocking of transmission." E. K.

The Effects of Aminophylline and Other Xanthines on the Pulmonary Circulation. Quimby, C. W. Jr., Aviado, D. M., Jr., and Schmidt, C. F.: J. Pharmacol. & Exper. Therap. **122**: 396, 1958.

The intravenous administration of aminophylline caused vasodilatation in the lungs and in the extremities of anesthetized dogs. Although the cardiac output was elevated, pulmonary blood flow was increased principally by local vasodilatation. This was determined by perfusing one lobe of the experimental dog lung with blood from a living donor dog and measuring the rate of blood flow before and after xanthine administration. Some 40 other xanthines were tested unsuccessfully in an effort to find a vasodilator which would act selectively on the pulmonary circulation. The relationship of chemical structure of various drugs to vasodilatation is discussed. E. K.

Cardiovascular Effects of Sympathomimetic Bronchodilators: Epinephrine, Ephedrine, Pseudoephedrine, Isoproterenol, Methoxyphenamine and Isoprophenamine. Aviado, D. M., Jr., Wnuck, A. L., and DeBeer, E. J.: J. Pharmacol. & Exper. Therap. **122**: 406, 1958.

The newer pharmacologic techniques for measurement were used to determine the tone of bronchial musculature, blood flow to systemic vascular beds, and cardiac functions in anesthetized dogs. Epinephrine, ephedrine, pseudoephedrine, isoproterenol, methoxyphenamine, and isoprophenamine were all administered to the same dog preparations in varying sequence. All of these drugs caused bronchodilatation when injected into the bronchial artery. When injected intravenously all of these drugs exhibited either hypertensive or hypotensive effects. "If sympathomimetic bronchodilatation is to be elicited without cardiovascular effects, it will have to be done by agents other than the six drugs we have used." It was noted that the vertebral blood vessels were constricted by ephedrine but dilated by pseudoephedrine. Bronchodilation was found to be equal for these two drugs in this study and it is believed that the latter drug is worthy of human trial. E. K.

Antihistaminic Drugs. Michelson, S. L., and Lowell, F. C.: New England J. Med. **258**: 994, 1958.

The antihistaminic properties of certain phenolic ethers have been recognized since 1937. Compounds of high activity and relatively low toxicity were introduced for clinical trial as early as 1942. The chemical core of the antihistamine compound is a substitute of ethylamine, $=CH_2\text{-}CH_2\text{-}N=$, which is also present in histamine. It is theorized that the antihistamine prevents the access of histamine to the tissue by competing with it at the receptor site.

The first carbon of the ethylamine group may be attached to a nitrogen, oxygen, or carbon, thereby forming an ethylenediamine, $=N\text{-}CH_2\text{-}CH_2\text{-}N=$, an aminoalkyl ether, $-O\text{-}CH_2\text{-}CH_2\text{-}N=$, or an alkylamine, $=CH_2\text{-}CH_2\text{-}CH_2\text{-}N=$, respectively. The antihistaminic properties of the three groups are comparable,

but those in the aminoalkyl ether group tend to cause a greater degree of central nervous system depression. Antihistaminic activity is also exhibited by aminoketones, secondary aminoalkylols, alkylesters, and haloalkylamines.

Antihistamine preparations block or interfere with the action of histamine on the vascular system, on smooth muscles of certain organs, and on the exocrine glands. The drugs are readily absorbed from the gastrointestinal tract and from injected sites. In general, the therapeutic effects are evident within one-half hour and the duration of action is probably not greater than four hours. Antihistamines are very effective in the treatment of allergic rhinitis and conjunctivitis, but they are of limited value in bronchial asthma. They may be of value in skin diseases associated with redness and itching and possibly in urticaria and angioneurotic edema. All antihistamines are capable of exerting some degree of local anesthetic action, which in itself may be responsible for their value in skin conditions.

With the administration of antihistamines, either depression or excitation of the central nervous system may occur. All preparations are capable of producing some degree of somnolence in some persons. Depression of the lower centers may also occur, exemplified by the effective application of these drugs in labryinthine disturbances and motion sickness. Additional side reactions vary with the individual and with the dose and include drowsiness, vomiting, dryness of the mouth, constipation, confusion, urinary frequency, excitability, and loss of judgment. Various cutaneous manifestations have also been reported. Isolated cases of respiratory distress and, more serious, blood dyscrasias have been cited. H. S.

Plasma Adrenocorticotrophic Hormone in Addison's Disease and Its Modification by the Administration of Adrenal Steroids. Bethune, J. E., Nelson, D. H., and Thorn, G. W.: J. Clin. Invest. **36**: 1701, 1957.

Blood levels of ACTH in human subjects were determined by a bio-assay technique. The subjects included 29 patients with Addison's disease, three bilaterally adrenalectomized patients, and, as controls, eight normal persons and eight hospitalized patients without endocrine disease. No measurable level of ACTH was found in the controls. ACTH levels were observable in the adrenal-insufficient group except for two cases of Addison's disease. In several instances repeated tests were necessary to reveal blood levels of ACTH. Hydrocortisone intravenously infused suppressed circulating ACTH levels, the effect persisting for 8 to 10 hours following the infusion. Limited testing of 9-alpha-fluorohydrocortisone and prednisolone indicated that they also inhibited ACTH secretion. Desoxycorticosterone had little effect, and progesterone had no effect on ACTH levels in one subject. E. K.

Myxedema Due to Iodine. DeVries, A., Levitus, Z., and Bakst, C.: Harefuah **54**: 170, 1958.

A 42-year-old asthmatic patient who had been taking 2 or 3 Gm. of potassium iodide daily at intermittent intervals over a five-year period developed signs and symptoms of myxedema and a marked goiter. The BMR was minus 30 per cent, and the blood cholesterol was 356 mg. per 100 c.c. Radioactive iodine uptake was 62 per cent after 2 hours and 80 per cent after 24 hours. When the medication was discontinued, all signs, symptoms, and laboratory findings of myxedema disappeared. Radioactive iodine uptake rose to 92 per cent after 24 hours and later became normal. After two months, the patient was given another tracer dose of I^{131}. One hour later 400 mg. of potassium

perchlorate was given orally and the radioactivity over the thyroid was measured for an hour at intervals of 10 minutes. There was a considerable and rapid decrease in the amount of radioactive iodine which had been previously absorbed by the gland, proving that a considerable part of the iodine remained in an inorganic form.

A 34-year-old woman who had had a subtotal thyroidectomy for thyrotoxicosis at the age of 27 developed myxedema a few months after the surgery. She was effectively treated for this condition with thyroid extract. For some unknown reason, this medication was discontinued, and she started to complain of dyspnea, for which she was given 1.0 Gm. of potassium iodide daily. Several months later, the patient developed symptoms of mild myxedema. On admission to the hospital, her BMR was minus 26 per cent and the blood cholesterol was 261 mg. per 100 c.c. The I^{131} uptake was 44 per cent in 24 hours (upper limit of normal). There was a marked clinical improvement when the potassium iodide was discontinued. The BMR became normal and the radioactive iodine uptake became normal after an initial rise.

The possible pathogenesis of this form of myxedema with hypometabolism, hypercholesteremia, and increased iodine uptake by the thyroid is discussed.

I. G.

A Contribution to the Pharmacodynamic Study of Histamine and Antihistamines in Big Animals. Desliens, L.: Presse méd. **66**: 562, 1958.

Bovine animals were found to be very sensitive to histamine, and as little as 25 mg. of histamine dihydrochloride could kill a cow of 500 kg. Within 30 seconds following an intravenous injection, the animals developed panting, blood hyperviscosity, and a pink discoloration of the mucous membranes. When Adrenaline was injected after the histamine it barely inhibited the histamine shock; however, when it was injected before the histamine it was effective. Ephedrine did not exhibit a similar effect. Cocaine and morphine, which are known to cause a marked rise in blood pressure in bovine and equine animals, failed to prevent the histamine shock but shortened the period of shock. Pilocarpine, eserine, and acetylcholine, which by themselves increase blood viscosity, did not markedly aggravate the shock, nor did atropine affect it significantly. Magnesium hyposulfite afforded no remarkable protection.

Animals were injected profusely with Locke's isotonic solution or a hypertonic solution of sodium chloride, glycerine, or saccharine, thus causing hemodilution and hypoviscosity. Histamine injected subsequently did not produce the expected hemoconcentration but the shock was the same. Hexamethonium did not prevent the histamine shock but Largactil did. Phenergan and Neo-Antergan were markedly protective against as much as 100 times the lethal dose of histamine.

I. G.

Immunology

Studies on the Mechanism of Hypersensitivity Phenomena. II. The Participation of Complement in Passive Cutaneous Anaphylaxis of the Albino Rat. Osler, A. G., Hawrisiak, M. M., Ovary, Z., Siqueira, M., and Bier, O. G.: J. Exper. Med. **106**: 811, 1957.

Passive cutaneous anaphylaxis was induced in rats by the intracutaneous injection of varying quantities of antisera (heated to 56° C. for 30 minutes). Two hours later the animals were given intravenous injections of antigen mixed with Evans blue dye. Reactions were measured by the spread of the blue dye in the skin of the animals sacrificed 60 minutes after antigen injection. Antigen systems used included chicken ovalbumin, horse antipneumococcus, and

rabbit antiribonuclease. The addition of complement from fresh guinea pig and rat sera enhanced the degree of reaction, both in normal rats and in rats rendered deficient in hemolytic complement. The enhancement factor appears to be related to the third component of the complement.

It is concluded that a significant effect on the immediate reaction of passive cutaneous anaphylaxis can be obtained by variation of antigen dose, antibody dose, and "a host factor which resembles hemolytic C'." E. K.

Studies on Antibody Synthesis Initiated In Vitro. Stevens, K. M., and McKenna, J. M.: J. Exper. Med. **107**: 537, 1958.

Rabbits were injected intravenously with endotoxin from *Salmonella typhosa* in order to enhance the subsequent antibody response. The animals were sacrificed 24 hours later. The spleens were removed, diced, and then incubated for one hour with bovine gamma globulin (BGG) or casein (control) in protein-free culture media. They were then carefully washed and incubated in media without antigen. At intervals the tissues were homogenized. Antibody determinations (modification of Boyden hemagglutination technique) were made on the media in which the cells had been suspended and on an extract of the tissue homogenate. The techniques used and numerous experiments relative to these techniques are described.

Antibody could be detected as early as one hour after exposure to antigen. Antibody was not formed when the BGG concentration was below 0.05 mg. per milliliter, irrespective of whether the animal had received BGG previously in vivo. Spleens from rabbits previously given BGG were able to produce antibody without endotoxin pretreatment. Endotoxin was essential to detectable antibody production by spleens from animals not previously given BGG. The quantity of antibody produced by BGG-pretreated animals was no greater than that produced by endotoxin-pretreated animals. The addition of autologous rabbit serum to the incubation medium increased antibody formation about 9 times over that produced by the tissue in protein-free medium. The addition of normal rabbit serum from rabbits either pretreated or not treated with endotoxin did not enhance antibody formation. The enhancing factor in autologous serum was nondialyzable, did not sediment at 105,000 g. for 2 hours, was stable overnight at 1° C., but labile to 56° C. for 30 minutes.

Under certain conditions splenic fragments were able to produce antibody to BGG. Antibody production was sharply inhibited by cortisone, prednisolone, and nitrogen mustard. E. K.

The Nature of Antigen-Antibody Complexes Formed in Rabbits During an Immune Response to Bovine Serum Albumin. Weigle, W. O.: J. Exper. Med. **107**: 653, 1958.

Bovine serum albumin labeled with I^{131} (IBSA) was injected intravenously into normal and x-radiated albino rabbits. The sera of these animals were analyzed for free antigen, antibody, alkali-precipitable material, and IBSA bound to globulin (antibody). There was no correlation between the presence or absence of alkali-precipitable material and the maximum antibody concentration. There was little IBSA in this material, and excess of antigen failed to dissolve the precipitate in these experiments. Irradiated rabbits did not develop alkali-precipitable material, and no circulating antigen-antibody complexes were found in their sera. It is suggested that, early in antibody formation, antigen is present in excess and complexes formed at this time may circulate for some time. When antibody response increases, the size of the complexes becomes so large that they are rapidly removed from circulation. "The pattern of the

appearance of circulating antigen-antibody complexes and the immune elimination of antigen probably depends on the amount of antigen injected, the rate of antibody synthesis, and perhaps the quality of antibody produced."

E. K.

Stimulating Action of Soluble Antigen-Antibody Complexes on Normal Guinea-Pig Smooth Muscle. Trapani, I. L., Garvey, J. S., and Campbell, D. H.: Science **127**: 700, 1958.

A pool of antiserum was obtained from rabbits which had been injected intravenously with recrystallized bovine serum albumin (BSA) over a period of about 4 weeks. Quantitative precipitin curves were obtained by combining 3 ml. of undiluted antiserum and 3 ml. of varying dilutions of BSA. The mixtures were kept for 48 hours at 4° C., centrifuged, and the clear supernates were separated. The precipitates were washed and analyzed for total nitrogen. The supernates were then tested by the Schultz-Dale technique on fresh duplicate strips of ileum from normal nonsensitized guinea pigs. After a 10-minute period, during which the contraction of the muscle strip was recorded, histamine was added to the bath to determine the maximal contraction. The stimulating action of the soluble antigen-antibody complex in the supernate was expressed as a percentage of the maximal contraction obtained with histamine.

The results indicated that the stimulating effect of the supernates was most active in the range of slight to moderate antigen excess. This effect was absent in the zone of antibody excess and minimal in the zone of extreme antigen excess. Muscles which contracted after an initial exposure to supernate, when washed and exposed again to the complex, failed to contract. This response suggested an immune reaction. A time lag of from 30 to 90 seconds between the addition of the complex to the bath and the contraction of the muscle, which does not occur with histamine or when antigen is added to sensitized tissue, suggested that the mechanism might be different. Control Schultz-Dale studies with rabbit antiserum alone, normal rabbit serum in varying amounts, bovine serum albumin alone, and mixtures of BSA and normal rabbit serum failed to evoke muscle contractions. The skin reactivity of the supernates was tested by their intracutaneous injection into normal guinea pigs previously treated with Evans blue. Generally, those supernates which elicited the most marked muscle contractions also elicited the most marked skin reactions.

B. S.

Miscellaneous

Fatal Massive Necrosis of the Liver as a Manifestation of Hypersensitivity to Probenecid. Reynolds, E. S., Schlant, R. C., Gonick, H. C., and Dammin, G. J.: New England J. Med. **256**: 592, 1957.

Fatal massive necrosis of the liver as a manifestation of hypersensitivity to probenecid was reported in a 75-year-old atopic man. This patient had had grand-mal seizures, bronchial asthma, and allergic rhinitis in the past. At the age of 65, he developed osteomyelitis of the left ninth rib and was treated with sulfadiazine and surgical resection. Following this, he developed a mild eosinophilia (14 per cent). At the age of 71, he developed gout and was treated with colchicine, a low-purine diet, and probenecid in doses of 0.5 Gm. twice a day. From 1952 through 1954, he experienced occasional acute attacks of gout and epileptic seizures which were treated with Dilantin and colchicine. He received probenecid from 1953 to 1955. In July of 1955, after relief from an acute attack of gout with colchicine, he was again given probenecid, 0.5

Gm. twice a day. Two days later he developed a nonproductive cough, wheezing, and a generalized pruritic rash. Subsequently, he developed a fever, yellow sputum, and persistent occipital headache. Chlor-tetracycline was administered and he was admitted to the hospital. On admission, the patient had a generalized cutaneous papular erythematous eruption, and purpuric areas were noted about the ankles. Icterus developed and the liver was found to be enlarged. He was treated with penicillin and streptomycin. Probenecid, phenobarbital, and Dilantin were discontinued. Laboratory evidence of hepatocellular dysfunction of marked degree was found, and a 15 per cent eosinophilia was noted. He improved gradually and was discharged after a month. Some time later, he was again started on probenecid and Dilantin. Two days later wheezing, a productive cough, headache, and generalized myalgia developed. Three days later anorexia, nausea, vomiting, fever, and a generalized pruritic erythematous rash were present. His urine became amber and icterus developed. Physical examination on admission to the hospital on this occasion showed him to be acutely ill, dehydrated, and markedly icteric. There was a maculopapular rash involving the tibial areas with petechiae. Spider angiomas and magenta palms were noted for the first time. Gradually, he developed signs and laboratory evidence of marked liver disease. This was accompanied by a 15 per cent blood eosinophilia. Gradually, evidence of liver injury increased, his general condition deteriorated, and he expired on the eleventh hospital day. Post-mortem examination revealed extensive, massive, liver necrosis and infiltration of this organ with large numbers of lymphocytes, eosinophils, and plasma cells. Eosinophilic infiltration of other organs, notably the kidneys, heart, lungs, and lymph nodes of the hilus of the liver, were found.

E. W.

Agranulocytosis After Promazine Therapy: Report of a Case. Chirico, A. M., Carfagno, S., and Lytel, F.: New England J. Med. **256**: 899, 1957.

Agranulocytosis following promazine (Sparine) therapy in a 46-year-old woman is reported. Promazine therapy had been started in doses of 150 mg. per day and had been rapidly increased to 800 mg. daily. Some 40 days prior to admission to the hospital, she had received a total dose of 19.5 Gm. No other drugs had been administered. When first seen, this patient had marked injection of the oropharynx, enlarged, tender anterior cervical lymph nodes, and enlarged external hemorrhoids. Her temperature was 103° F. The blood pressure was 172/84. Initially, the white count was 750 and consisted only of lymphocytes. A bone-marrow specimen obtained from the iliac crest revealed a marked reduction of granulocytes. There was an arrest of myelopoiesis at the premyelocyte stage. Two days after admission, the patient complained of severe perianal pain and rectal tenesmus. Examination revealed acute inflammation of the external hemorrhoids and extensive erythema and induration of the perianal area. The temperature remained at 103° F. Treatment consisted of large doses of antibiotics (streptomycin, penicillin, tetracycline), cortisone, sitz baths, and other supportive therapy. On the eighth hospital day, there was a slough of the perianal area on the right side. The temperature rose to 105° F., but as granulocytes appeared in the peripheral blood and increased in size and in numbers of mature cells, there was gradual subsidence of the fever and an uneventful recovery.

E. W.

A New Concept in the Treatment of Penicillin Reactions: Use of Penicillinase. Becker, R. M.: Ann. Int. Med. **48**: 1228, 1958.

Penicillinase is an enzyme which can be obtained from several strains of bacteria, including staphylococci, *Escherichia coli,* and the *Bacillus cereus.*

This enzyme inactivates penicillin through its catalytic hydrolysis of the lactam ring of the penicillin molecule, changing penicillin to penicilloic acid which is nonantigenic in this sensitivity system.

The author has collected the data on 46 patients from various sections of the country who had suffered from penicillin reactions and who were treated with penicillinase. Certain of the patients had previously received antihistaminics and/or ACTH and the steroids. Others were treated with penicillinase alone, and still others received penicillinase concomitantly with one of the other medications. Twenty of the 46 patients had favorable results which could be directly attributed to the penicillinase. It appears that the medication, when given early in the reaction, has a greater chance for effectiveness. Only two cases in the series had a poor response, and in each of these the penicillinase was given weeks to months after the reactions started. In the entire series of cases there were no systemic reactions to either single or multiple injections of the drug. Local pain at the site of injection was not uncommon. H. F.

Agranulocytosis in the Course of a Chlorpromazine Treatment. A New Case: Cure. Millon, R., Landry, M., and Billaud, R.: Presse méd. **66**: 28, 1958.

A 56-year-old manic-depressive patient was treated with Largactil and developed benign reactions in the form of a reversible extrapyramidal syndrome and allergic skin reactions. Another course of large doses of Largactil was given for a subsequent seizure. One month after the beginning of the treatment, she developed an acute pharyngitis and agranulocytosis. Successful therapy consisted of penicillin, steroids, pentose nucleotides, vitamins, and transfusions. The authors stress the importance of a complete blood count at least once a month during chlorpromazine treatment. I. G.